REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein, does not raise any new issue requiring further search and/or consideration as the amendments amplify issues previously discussed throughout prosecution and does not present any additional claims. The Amendment is necessary and was not earlier presented because it is made in response to arguments raised in the final rejection. Entry of the Amendment is thus respectfully requested.

The Office Action Summary indicates that claims 1-24, 27 and 28 are pending. Claims 1, 21-24 and 27 have been amended to recite separating fragments "by capillary electrophoresis, thereby determining the length of each fragment". Basis for these amendments may be found on page 3, paragraph 2, of the present specification. Thus, the Amendments to the claims do not introduce any prohibited new subject matter. Applicants reserve the right to file a continuation or divisional application directed to any subject matter canceled by way of this Amendment.

Rejection under 35 U.S.C. § 103(a)

Claim 1

Claim 1 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* (WO 95/04160). The Office Action asserts that it would have been purportedly obvious to the skilled artisan to apply the detection of mass labels in the method Southern *et al.* where unique labels are attached to features of known lengths and

multiple labeled features are ligated to form a fragment to detect the labels and relate the labeled features to the length of the fragment. Applicants respectfully traverse.

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re* Dow Chemical Co., . . . 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited reference does not teach or suggest the claimed invention or give the skilled artisan an expectation that the claimed method could be conducted with a reasonable expectation of success.

The Office Action notes that the method of claim 1 has been broadly construed. For purposes of clarification, step (ii) of claim 1 has been amended by way of the present Amendment to recite the separation of the claimed fragments by capillary electrophoresis, thereby determining the length of each fragment. As discussed in the present specification on page 3, capillary electrophoresis systems are very amenable to microfabrication, and

thus avoid problems associated with conventional gel electrophoresis. For example, conventions gel electrophoresis often requires a long time, often hours, for the separation of bands. This is because conventional techniques require the limited step of resolution of the fragment population generated by the polymerization in the presence of blocking nucleotides. In a microfabricated capillary, the time required to run a gel can be minutes rather than hours resulting in increased throughput. Further, the separation media used with capillary gel electrophoresis systems can be liquid, allowing automated loading of capillaries.

Thus, the method of the claimed invention avoids the problems associated with the conventional methods of gel electrophoresis. Because the speed of the claimed method is fast, the method reduces the time available for secondary structure formation in the templates, which could later impede chemical and biological steps necessary to sequencing.

In contrast to the claimed invention, as amended herein, Southern *et al.* do not teach or suggest the use of capillary electrophoresis for the separation of fragments. Southern *et al.* disclose a method of labeling an analyte molecule with a cleavable tag linked to the analyte molecule at a designated position, wherein the tag has one or more reporter groups. Southern applies the method to sequence a nucleic acid and to sequence multiple nucleic acid templates. Specifically, Southern *et al.* disclose a moderately large labeled nucleic acid template hybridised with an array of short oligonucleotide probes under very stringent hybridisation conditions. However, Southern's method does not determine the length of the labeled template, which corresponds to the DNA being sequenced in the claimed method. In Southern's method, the length of the template must be known in advance, at least to the

extent that it must be shorter than an upper limit. The position of oligonucleotide subsequences is inferred from the number of cycles of ligation and the measurements that have already taken place. Therefore, Southern *et al.* do not disclose a step of separating the fragments on the basis of their length.

In contrast, for the claimed invention, it is the differences in length between the fragments of the template that allow their separation. Further, as amended herein, claim 1 specifically recites a step determining and measuring the lengths of the claimed fragments.

There would have been no motivation or reason for modifying Southern's method by incorporating a step of separating template fragments on the basis of their length via capillary gel electrophoresis. Southern *et al.* not only fails to disclose or suggest the use of the this type of gel electrophoresis, but does not provide the motivation to use this technique. Rather, Southern *et al.* encourage the use of hybridisation techniques to separate out the fragments. As a result, applicants submit that claim 1 would not have been obvious over Southern *et al.*

Thus, Applicants respectfully submit that they have met the burden of showing that the claimed method is different from and non-obvious in light of the cited reference. Withdrawal of this rejection is respectfully requested.

Claims 2-18 and 20-26

Claims 2-18 and 10-26 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Ness *et al.* (U.S. Patent No. 6,027,890) and Alberts (*Molecular Biology of the Cell* (1994), 298). These references are cited for

purportedly disclosing that primer extension dideoxynucleotide incorporation provides a series of fragments that contain all possible lengths of template. The Office Action asserts that it would have been obvious to the skilled artisan to modify the population of DNA fragments of Southern *et al.* and to provide fragments containing all possible lengths as disclosed by Ness *et al.* and Alberts.

Applicants respectfully traverse. As discussed above, claim 1, as well as claims 21-24 and 27, have been amended to clearly recite the separation of the fragments by size via capillary gel electrophoresis. Rejected claims 2-18 and 20-26 depend on one of the amended claims. In contrast to the claimed invention, as amended herein, Southern *et al.* do not teach or suggest the use of capillary electrophoresis for the separation of fragments. The additional cited references, Ness *et al.* and Alberts, fail to remedy the deficiencies of Southern *et al.*

In addition, the combination of the three cited references does not indicate specifically how a probe should be labeled and used such that the multiple labeled probes could be used simultaneously to sequence many templates at once. In addition, there is no motivation to combine the three cited references to reach the claimed invention. In fact, Southern *et al.* actually teaches away from the methods disclosed by Ness and Alberts, because Southern teaches that the advantage of its hybridisation based method is that it avoids a need to determine the length of the DNA. Southern also discloses that gel based methods, such as the electrophoretic and chromatographic method of Ness cannot support the same degree of parallelism or throughput as array based methods.

Thus, Applicants respectfully request that the rejection be withdrawn.

Claim 19

Claim 19 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Smith (*Nature* (1991), 349:812-813). Smith is cited for purportedly disclosing that capillary electrophoresis provides for rapid analysis of long DNA sequences.

Applicants respectfully note that there would have been no motivation to combine Southern *et al.* and Smith, because Southern *et al.* disclose that the advantage of the hybridisation based method is that it avoids a need to determine the length of the DNA. Southern also discloses that gel based methods, such as the electrophoretic and chromatographic method of Smith, cannot support the same degree of parallelism or throughput as array based methods. The Office Action states that Southern *et al.* discloses the benefits of gels on page 22, lines 10-12, which state that the longer continuous lengths of fragments can be read on a gel. However, lines 13-19 of page 22 of Southern *et al.* go on to state that "This advantage for gels would, of course, be lost if the sequence read from the array could be extended by further rounds of analysis. But the fundamental advantage of array-based approaches is the parallelism which enables thousands of templates to be analyzed together; the number that can be analysed on a gel is limited by the width of the gel to less than fifty". Thus, Applicants submit that upon reading Southern *et al.* the skilled artisan would be motivated to avoid combing Smith with Southern *et al.* Thus, Applicants respectfully request that the rejection be withdrawn.

Claims 27-28

Claims 27-28 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Ness *et al.* Applicants respectfully traverse. As discussed above, claim 27 has been amended to clearly recite the separation of the fragments by size via capillary gel electrophoresis. In contrast to the claimed invention, as amended herein, Southern *et al.* do not teach or suggest the use of capillary electrophoresis for the separation of fragments. The additional reference, Ness *et al.*, fails to remedy the deficiencies of Southern *et al.* Thus, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment and Reply under 37 C.F.R. § 1.116 dated April 26, 2002

Marked-Up Claims 1, 21-24 and 27

1. (Twice Amended) A method for characterizing DNA, which comprises:

(i) providing a population of fragments of said DNA, each fragment having cleavably attached thereto a mass label for identifying a feature of that fragment;

(ii) separating the fragments [on the basis of their length] by capillary electrophoresis, thereby determining the length of each fragment;

(iii) cleaving each fragment in a mass spectrometer to release its mass label; and

(iv) determining each mass label by mass spectrometry to relate the feature of each fragment to the length of the fragment in order to characterize said DNA

21. (Twice Amended) A method for characterising DNA, which comprises

(a) providing a primed DNA single-stranded template;

(b) contacting the template in the presence of DNA polymerase with a mixture of nucleotides for hybridising to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the templates in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but reversibly blocked to prevent further polymerisation thereto, wherein the step of contacting forms a series of templates containing all possible lengths of the second strand of DNA, each second strand terminated with one of the probes;

(c) removing unincorporated nucleotides;

(d) unblocking the modified nucleotides;

(e) contacting the series of templates with an array of oligonucleotide probes to form a series of fragments, each oligonucleotide probe having a nucleotide sequence of common length 2 to 6, and all combinations of sequences being present in the array, wherein each probe is cleavably attached to a mass label uniquely resolvable in mass spectrometry for identifying the nucleotide sequence;

(f) separating the fragments [from one another on the basis of their length] by capillary electrophoresis, thereby determining the length of each fragment;

(g) cleaving each fragment to release its mass label; and

(h) determining each mass label by mass spectrometry to relate a nucleotide sequence that corresponds to the mass label to a position in the template so as to deduce the sequence of the template in order to characterise the DNA.

22. (Twice Amended) A method for characterising DNA, which comprises

(a) providing a plurality of primed DNA single-stranded templates, each at a unique concentration;

(b) contacting the templates in the presence of DNA polymerase with a mixture of nucleotides for hybridising to the template for forming a second strand of DNA complementary to the templates, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the templates in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second

strand of DNA but reversibly blocked to prevent further polymerisation thereto, wherein the step of contacting forms a series of templates containing all possible lengths of the second strand of DNA, each second strand terminated with one of the probes;

(c) removing unincorporated nucleotides;

(d) unblocking the modified nucleotides;

(e) contacting the series of templates with an array of oligonucleotide probes to form a series of fragments, each oligonucleotide probe having a nucleotide sequence of common length 2 to 6, and all combinations of sequences being present in the array, wherein each probe is cleavably attached to a mass label uniquely resolvable in mass spectrometry for identifying the nucleotide sequence;

(f) separating the fragments [from one another on the basis of their length] by capillary electrophoresis, thereby determining the length of each fragment;

(g) cleaving each fragment to release its mass label; and

(h) determining the identity and amount of each mass label by mass spectrometry to relate a nucleotide sequence of a probe that corresponds to the mass label to a position in its respective template so as to deduce the sequence of the template in order to characterise the DNA.

23. (Twice Amended) A method for characterising DNA, which comprises

(a) providing a primed DNA single-stranded template;

(b) contacting the template in the presence of DNA ligase with a mixture of oligonucleotides for hybridising to the template for forming a second strand of DNA

complementary to the template, the oligonucleotides each having a common length in the range 2 to 6, wherein the mixture further comprises a set of probes containing all possible oligonucleotides of the common length L for hybridising to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a corresponding mass label uniquely resolvable in mass spectrometry for identifying the modified oligonucleotide, wherein the step of contacting forms a series of fragments containing all possible lengths of the second strand of DNA of integer multiples of L, each fragment terminated with one of the probes;

(c) separating the fragments [from one another on the basis of their length] by capillary electrophoresis, thereby determining the length of each fragment;

(d) cleaving each fragment to release its mass label; and

(e) determining each mass label by mass spectrometry to relate its corresponding oligonucleotide to a position in the template so as to deduce the sequence of the template in order to characterise the DNA.

24. (Twice Amended) A method for characterising DNA, which comprises

(a) providing a plurality of primed DNA single-stranded templates, each at a unique concentration;

(b) contacting the templates in the presence of DNA ligase with a mixture of oligonucleotides for hybridising to the templates for forming a second strand of DNA complementary to the templates, the oligonucleotides each having a common length in the

range 2 to 6, wherein the mixture further comprises a set of probes containing all possible oligonucleotides of the common length L for hybridising to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a corresponding mass label uniquely resolvable in mass spectrometry for identifying the modified oligonucleotide, wherein the step of contacting forms a series of fragments containing all possible lengths of the second strand of DNA of integer multiples of L, each fragment terminated with one of the probes;

(c) separating the fragments [from one another on the basis of their length] by capillary electrophoresis, thereby determining the length of each fragment;

(d) cleaving each fragment to release its mass label; and

(e) determining the identity and amount of each mass label by mass spectrometry to relate its corresponding oligonucleotide to a position in its respective template so as to deduce the sequence of the template in order to characterise the DNA.

27. (Once Amended) A method for characterizing DNA, which comprises:

(a) providing at least one DNA single-stranded template primed with a primer;

(b) generating a population of fragments of said DNA from the at least one template by contacting the at least one template in the presence of DNA polymerase with a mixture of nucleotides for hybridising to the at least one template for forming a second strand of DNA complementary to the at least one template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the at least one template

in which the nucleotide of each probe comprises a modified nucleotide or oligonucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto, which modified nucleotide or oligonucleotide is cleavably attached to the mass label for identifying the modified nucleotide or oligonucleotide, which mass label is cleavable from the probe in a mass spectrometer and is resolvable by mass spectrometry, and wherein each fragment is terminated with one of the probes, wherein the population comprises at least one series of DNA fragments, the or each series containing all possible lengths of a second strand of DNA complementary to the or each template;

(c) separating the fragments [on the basis of their length] by capillary electrophoresis, thereby determining the length of each fragment;

(d) cleaving each fragment in a mass spectrometer to release its mass label; and

(e) determining each mass label by mass spectrometry to relate a terminating modified nucleotide or oligonucleotide of each fragment to the length of the fragment in order to characterize said DNA.